Day : Tuesday
Date: 7/13/2004

Time: 15:10:38

PALM INTRANET

Inventor Information for 10/800918

Inventor Name	City	State/Country
SINGER, CLAUDE	KFAR SABA	ISRAEL
LIBERMAN, ANITA	TEL AVIV	ISRAEL
FINKELSTEIN, NINA	HERZLIYA	ISRAEL

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data

Search Another: Application# Search **or Patent#** Search

PCT / / Search **or PG PUBS #** Search

Attorney Docket # Search

Bar Code # Search

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L Number	Hits	Search Text	DB	Time stamp
1	183	540/578	USPAT	2004/07/13 15:09
2	268187	crystall$	USPAT	2004/07/13 15:09
4	118	540/578 and crystall$	USPAT	2004/07/13 15:09
3	85	mirtazapine$	USPAT	2004/07/13 15:09
5	5	mirtazapine$ and (540/578 and crystall$)	USPAT	2004/07/13 15:09

L1 STRUCTURE UPLOADED

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L1 HAS NO ANSWERS
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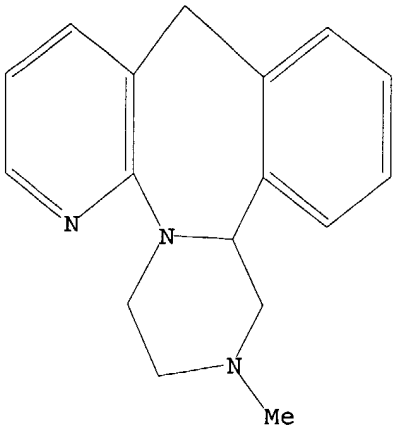

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SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 33 TO 447
PROJECTED ANSWERS: 3 TO 163

L2 3 SEA SSS SAM L1

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FULL SCREEN SEARCH COMPLETED - 223 TO ITERATE

100.0% PROCESSED 223 ITERATIONS 53 ANSWERS
SEARCH TIME: 00.00.01

L3 53 SEA SSS FUL L1

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COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 148.15 148.36

FILE 'CAPLUS' ENTERED AT 15:15:23 ON 15 SEP 2003
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FILE COVERS 1907 - 15 Sep 2003 VOL 139 ISS 12
FILE LAST UPDATED: 14 Sep 2003 (20030914/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L4 311 L3

=> s l4 and crystall?
L5 9 L4 AND CRYSTALL?

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L5 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:570816 CAPLUS
DOCUMENT NUMBER: 139:138735
TITLE: Sedative non-benzodiazepine formulations
INVENTOR(S): O'Toole, Edel; Fogarty, Siobhan
PATENT ASSIGNEE(S): Biovail Laboratories Inc., Barbados
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003059349	A1	20030724	WO 2003-IE1	20030109
W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003165566	A1	20030904	US 2003-338876	20030109

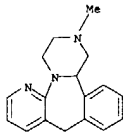
PRIORITY APPLN. INFO.: US 2002-346613P P 20020110

AB The invention provides for an enhanced absorption pharmaceutical composition comprising a plurality of microparticles, each microparticle comprising at least one sedative non-benzodiazepine, at least one spheronisation aid, and at least one solubility enhancer. The microparticles of the invention are further incorporated into an oral fast-dispersing dosage form. For example, microparticles were prepared containing zolpidem tartrate 15%, Gelucire 50/13 35%, and distilled monoglyceride (Myvaplex) 50%. Microparticles obtained were then coated for taste masking with a coating solution containing a 60:30:10 ratio of Eudragit NE30D, talc, and Methocel. The coated microparticles were used for preparation of tablets.

IT **85650-52-8**, Mirtazapine
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of microparticles for enhanced oral bioavailability of non benzodiazepine sedatives)

RN 85650-52-8 CAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b hexahydro-2-methyl- (9CI) (CA INDEX NAME)

L5 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:282146 CAPLUS
DOCUMENT NUMBER: 138:304301
TITLE: Novel synthesis and **crystallization** of piperazine ring-containing compounds such as mirtazapine
INVENTOR(S): Singer, Claude; Liberman, Anita; Finkelstein, Nina
PATENT ASSIGNEE(S): Israel
SOURCE: U.S. Pat. Appl. Publ., 9 pp., Cont. in-part of U.S. Ser. No. 552,485.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003069417	A1	20030410	US 2002-206344	20020729
US 2001051718	A1	20011213	US 2001-900646	20010706
US 6545149	B2	20030408		
US 2003088094	A1	20030508	US 2002-283093	20021030
US 6576764	B2	20030610		
US 2003120068	A1	20030626	US 2003-348757	20030123
US 2003135043	A1	20030717	US 2003-368441	20030220

PRIORITY APPLN. INFO.: US 1999-130047P P 19990419
US 2000-182745P P 20000216
US 2000-552485 A2 20000418
US 2001-900646 A3 20010706
US 2002-283093 A3 20021030

OTHER SOURCE(S): CASREACT 138:304301; MARPAT 138:304301
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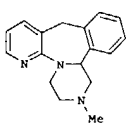
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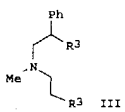
II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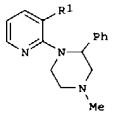
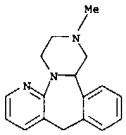

IV

AB Mirtazapine (I) was prepared by reacting substituted pyridine II [R1 = CH2OH, CH2Cl, CH2Br, CH2I; R2 = NH2] with compound III [R3 = Cl, F, Br, I]

L5 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)
followed by treating the resulting piperazine IV with ring closing reagent, such as H2SO4. The mirtazapine intermediate IV (R1 = CO2H) may be prepd. by hydrolyzing IV (R1 = CN) with KOH at a temp. of at least about 140°C. New processes for recrystn. of I form crude mirtazapine are also disclosed. The present invention also relates to **cryst.** adducts of mirtazapine and water, preferably contg. up to about 3.5% by wt. water, pharmaceutical compns. contg. the **cryst**. adducts, and methods of treating depression by administering such compns.

IT **341512-90-1P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and **crystallization** of mirtazapine water adduct)

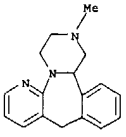
RN 341512-90-1 CAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,4a,9-hexahydro-3-methyl-, hydrate (9CI) (CA INDEX NAME)



●x H_2O

IT **85650-52-8P**, Mirtazapine
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and **crystallization** of piperazine ring-containing compds. such as mirtazapine)

RN 85650-52-8 CAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



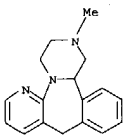
L5 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)

L5 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:406942 CAPLUS
DOCUMENT NUMBER: 136:401782
TITLE: Process for the manufacture of anhydrous, solvent-free mirtazapine crystals
INVENTOR(S): Maeda, Chiharu; Yoshikawa, Sadanobu; Iishi, Eiichi
PATENT ASSIGNEE(S): Sumika Fine Chemicals Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

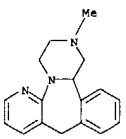
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1209159	A2	20020529	EP 2001-111102	20010508
EP 1209159	A3	20030305		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002065413	A1	20020530	US 2001-842871	20010427
AU 2001040301	A5	20020606	AU 2001-40301	20010430
JP 2002220390	A2	20020809	JP 2001-291863	20010925

PRIORITY APPLN. INFO.: JP 2000-359891 A 20001127
OTHER SOURCE(S): CASREACT 136:401782
AB Methods for producing anhydrous mirtazapine crystals that are either (1) substantially free of lower alc. insolubles or (2) substantially free of residual solvent, and which have an average particle diameter of from 10-50 μm, are described where: one filters a lower alc. (e.g., methanol) solution of crude mirtazapine to provide a filtrate; concentrating the filtrate to provide a concentrated filtrate; and **crystallizing** the anhydrous mirtazapine from the concentrated filtrate using a precipitation solvent selected from heptane and petroleum ethers.
IT **85650-52-8P**, Mirtazapine
RL: IMF (Industrial manufacture); PEP (Physical, engineering or chemical process); PRP (Properties); PUR (Purification or recovery); PYP (Physical process); PREP (Preparation); PROC (Process)
(process for the manufacture of anhydrous solvent-free mirtazapine crystals)
RN 85650-52-8 CAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)

L5 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)



L5 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:880108 CAPLUS
DOCUMENT NUMBER: 136:268247
TITLE: Spectroscopic methods for determining enantiomeric purity and absolute configuration in chiral pharmaceutical molecules
AUTHOR(S): Shah, Rekha D.; Nafie, Laurence A.
CORPORATE SOURCE: The RW Johnson Pharmaceutical Research Institute, Spring House, PA, 19477-0776, USA
SOURCE: Current Opinion in Drug Discovery & Development (2001), 4(6), 764-775
CODEN: CODDFF; ISSN: 1367-6733
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with refs. Anal. support, such as methods development, along with identification and characterization of intermediates and impurities, are critical in the development of a chemical process. The preparation of a drug substance requires the development of anal. methods for monitoring reactions and identifying impurities. Methods development for a chiral drug mol. is more difficult as the method must be capable of monitoring the overall reaction as well as possible racemization of starting materials and products. Chiral methods are often required to monitor the reaction steps of a synthesis, however, the development of enantiomeric purity methods are time-consuming and expensive. The use of chiroptical detectors, such as CD (CD), optical rotation (OR) and vibrational CD (VCD), can help to reduce or eliminate the need to develop chiral monitoring methods and also to predict absolute configuration. Recently, VCD has shown remarkable success with the latter and currently holds the most promise as a general, direct method that can be used as an alternative to X-ray **crystallog.** Each of the mentioned techniques can help anal. chemists to reduce the time associated with traditional enantiomeric purity methods development and to determine absolute configuration. This review will discuss the scope and limitations of these techniques for the rapid and routine determination of both enantiomeric excess and absolute configuration.
IT **85650-52-8**, Mirtazapine
RL: ANT (Analyte); ANST (Analytical study)
(spectroscopic methods for determining enantiomeric purity and absolute configuration in chiral pharmaceuticals)
RN 85650-52-8 CAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



L5 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS
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L5 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:435071 CAPLUS
DOCUMENT NUMBER: 135:33494
TITLE: Process for the preparation of a pyridinemethanol compound
INVENTOR(S): Iishi, Eiichi; Yoshikawa, Kanami
PATENT ASSIGNEE(S): Sumika Fine Chemicals Co., Ltd., Japan
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001042240	A1	20010614	WO 2000-JP6688	20000928
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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WO 2001042239	A1	20010614	WO 2000-JP5384	20000811
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EP 1238977	A1	20020911	EP 2000-962909	20000928
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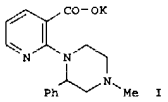
PRIORITY APPLN. INFO.:
JP 1999-353514 A 19991213
WO 2000-JP5384 W 20000811
WO 2000-JP6688 W 20000928

OTHER SOURCE(S): CASREACT 135:33494
GI



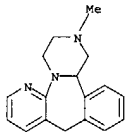
I

L5 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)

AB A pyridinemethanol compound useful as an important intermediate for the preparation of mirtazapine effective as an antidepressant can be prepared by reducing a potassium salt of pyridinecarboxylic acid as represented by formula I with a metal hydride. Thus, 1-butanol 162, KOH 60.93, and 2-(4-methyl-2-phenylpiperazin-1-yl)pyridine-3-carbonitrile oxalate 40 g were heated to give potassium 2-(4-methyl-2-phenylpiperazin-1-yl)pyridine-3-carboxylate, which was reduced in THF with 12.5 g lithium aluminum hydride to give 21.78 g 2-(4-methyl-2-phenylpiperazin-1-yl)pyridine-3-methanol (yield 70.78%).

IT **85650-52-8P**, Mirtazapine
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of pyridinemethanol compound as intermediate for mirtazapine)

RN 85650-52-8 CAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L5 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:435070 CAPLUS
DOCUMENT NUMBER: 135:33493
TITLE: Process for the preparation of a pyridinemethanol compound
INVENTOR(S): Iishi, Eiichi; Yoshikawa, Kanami
PATENT ASSIGNEE(S): Sumika Fine Chemicals Co., Ltd., Japan
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001042239	A1	20010614	WO 2000-JP5384	20000811
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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WO 2001042240	A1	20010614	WO 2000-JP6688	20000928
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EP 1238977	A1	20020911	EP 2000-962909	20000928
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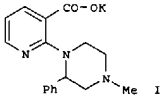
US 6376668	B1	20020423	US 2000-706803	20001107
US 2002035255	A1	20020321	US 2001-981919	20011019
US 6437120	B2	20020820		

PRIORITY APPLN. INFO.:
JP 1999-353514 A 19991213
WO 2000-JP5384 W 20000811
WO 2000-JP6688 W 20000928
US 2000-706803 A3 20001107

OTHER SOURCE(S): CASREACT 135:33493
GI



I

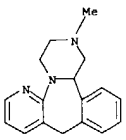
L5 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)

AB A pyridinemethanol compound serving as an important intermediate of mirtazapine useful as antidepressant can be prepared by reducing a potassium salt of a pyridinecarboxylic acid as represented by formula I with a metal hydride.

IT **85650-52-8P**, Mirtazapine
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of pyridinemethanol compound as intermediate for mirtazapine)

RN 85650-52-8 CAPLUS

CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2001:396868 CAPLUS
DOCUMENT NUMBER: 135:12412
TITLE: Anhydrous mirtazapine crystals and process for producing the same
INVENTOR(S): Iishi, Eiichi; Imamiya, Yoshiyuki
PATENT ASSIGNEE(S): Sumika Fine Chemicals Co., Ltd., Japan
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001038329	A1	20010531	WO 2000-JP4835	20000719
W: AU, CA, IN, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 2000060199	A5	20010604	AU 2000-60199	20000719
WO 2001038330	A1	20010531	WO 2000-JP6687	20000928
W: AU, CA, IN, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 2000074471	A5	20010604	AU 2000-74471	20000928
AU 763502	B2	20030724		
EP 1225174	A1	20020724	EP 2000-962908	20000928
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
US 2002103372	A1	20020801	US 2002-41495	20020110
US 6552189	B2	20030422		
US 2003130504	A1	20030710	US 2003-337277	20030107

PRIORITY APPLN. INFO.:
JP 1999-333049 A 19991124
JP 2000-67476 A 20000310
WO 2000 JP4835 W 20000719
WO 2000-JP6687 W 20000928
US 2000-697329 A3 20001027
US 2002-41495 A3 20020110

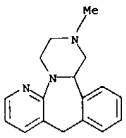
AB This document discloses : lowly-hygroscopic anhydrous mirtazapine crystals showing moisture absorption of 0.6 weight% or less when stored in the air at 25°C, at a relative humidity of 75% under atmospheric pressure for 500 h; a process for producing anhydrous mirtazapine crystals showing moisture absorption of 0.6 weight% or less when stored in the air at 25°C at a relative humidity of 75% under atmospheric pressure for 500 h characterized by drying crystals of mirtazapine hydrate; and a process for producing crystals of mirtazapine hydrate characterized by **crystallising** crude mirtazapine by using a water soluble polar organic solvent and water. By using this production method, stable anhydrous mirtazapine having little hygroscopicity can be produced by a convenient industrial method. The anhydrous mirtazapine

L5 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)
crystals are usable as active ingredients in an antidepressant.

IT **341512-89-8 341512-90-1**
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PROC (Process)
(preparation of anhydrous mirtazapine crystals)

RN 341512-89-8 CAPLUS

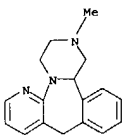
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,4a,9-hexahydro-3-methyl-, hydrate (2:1) (9CI) (CA INDEX NAME)



●1/2 H_2O

RN 341512-90-1 CAPLUS

CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,4a,9-hexahydro-3-methyl-, hydrate (9CI) (CA INDEX NAME)



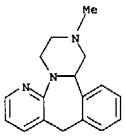
●x H_2O

IT **85650-52-8P**, Mirtazapine
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of anhydrous mirtazapine crystals)

RN 85650-52-8 CAPLUS

CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)

L5 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

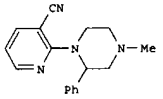
L5 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:265372 CAPLUS
DOCUMENT NUMBER: 134:280862
TITLE: Process for the preparation of a piperazine derivative
INVENTOR(S): Maeda, Chiharu; Iishi, Eiichi; Wang, Weigi; Imamiya, Yoshiyuki
PATENT ASSIGNEE(S): Sumika Fine Chemicals Co., Ltd., Japan
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001025185	A1	20010412	WO 2000-JP5432	20000814
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
WO 2001023345	A1	20010405	WO 2000-JP6650	20000927
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1136470	A1	20010926	EP 2000-962874	20000927
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AU 751629	B2	20020822	AU 2000-74455	20000927
US 6495685	B1	20021217	US 2000-697140	20001027

PRIORITY APPLN. INFO.: JP 1999-280378 A 19990930
WO 2000-JP5432 W 20000814
WO 2000-JP6650 W 20000927

OTHER SOURCE(S): CASREACT 134:280862
GI

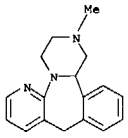
L5 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)



I

AB A process for the preparation of a piperazine derivative, namely 2-(4-methyl 3-phenylpiperazin-1-yl) 3-cyanopyridine (I), comprises reacting 1-methyl-3-phenylpiperazine with 2-chloro-3-cyanopyridine in the presence of a base and an alkali metal halide in an aprotic polar organic solvent. This piperazine derivative I and its oxalate are useful as intermediates for the preparation of mirtazapine. Thus, 11.4 kg N-methylethanolamine was added dropwise to a solution of 20 kg styrene oxide in 38 kg DMF at .apprx.80°, stirred at .apprx.80° for 3 h, and cooled to room temperature to give a DMF solution of N-(2-hydroxyethyl)-N-methyl-2-hydroxy-2-phenylethylamine which was added dropwise to a solution of 45 kg SOCl2 in 67.4 kg toluene at 0-25°, stirred at 45-55° for 2 h, cooled at ≤25°, treated dropwise with 95 kg H2O and then with 30 weight% aqueous KOH at 0-25°, and left to stand for phase separation The organic and aqueous phase were separated and the aqueous phase was extracted with 55 kg toluene, followed by combining the extract and the organic phase, drying over 4.8 kg MgSO4, treating with 4.8 kg activated clay and filtration, and washing with 19.9 kg PhMe to give a toluene solution of N-(2-chloroethyl)-N-methyl-2-chloro-2-phenylethylamine (II). To the toluene solution was introduced 5.5 kg HCl(g) at 10-35° and stirred at 20-25° for 2 h and the precipitated crystals were filtered and washed with 69 kg toluene to give 30 kg II.HCl. EtOAc (100 mL), 460 mg Bu4NBr, and 20.1 g II.HCl were added to 132 g 28% aqueous NH3 at room temperature and stirred at 40-45° for 3 h, followed by separating the organic layer and extracting the aqueous layer with EtOAc (2 + 30 mL) and the combined organic layer evaporated in vacuo to give 53.8% 1-methyl-3-phenylpiperazine (III) (7.1 g). III 5.51, 2-chloro-3-cyanopyridine 4.47, Et3N 4.1, and KI 5.20 g were added to 11 mL DMF and stirred at 125-130° for 24 h, followed by removing Et3N and DMF under reduced pressure, adding 20 mL H2O and 25 mL EtOAc to the residue, adjusting pH at 8-9 with 10% NaOH, separating the organic phase, and extracting the aqueous layer with EtOAc (3 + 30 mL), washing the combined the organic layer with 5% NaHCO3, drying and concentration, and crystallization from

L5 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)
petroleum ether 36% I (3.14 g, 97.1% purity).
IT **85650-52-8P**, Mirtazapine
RL: PNU (Preparation, unclassified); PREP (Preparation)
(preparation of (methylphenylpiperazinyl)cyanopyridine as intermediate for mirtazapine)
RN 85650-52-8 CAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



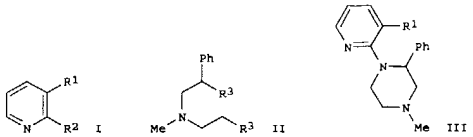
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L5 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:756528 CAPLUS
DOCUMENT NUMBER: 133:321900
TITLE: Novel synthesis and **crystallization** of piperazine ring-containing compounds such as mirtazapine
INVENTOR(S): Singer, Claude; Liberman, Anita; Finkelstein, Nina
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals Usa, Inc.
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000062782	A1	20001026	WO 2000-US10357	20000418
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1178805	A1	20020213	EP 2000-923457	20000418
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
HR 2001000747	A1	20021231	HR 2001-747	20011015
US 2003088094	A1	20030508	US 2002-283093	20021030
US 6576764	B2	20030610		
US 2003120068	A1	20030626	US 2003-348757	20030123

PRIORITY APPLN. INFO.: US 1999-130047P P 19990419
US 2000-552485 A3 20000418
WO 2000-US10357 W 20000418
US 2001-900646 A3 20010706
US 2002-283093 A3 20021030

OTHER SOURCE(S): CASREACT 133:321900; MARPAT 133:321900
GI



I II III

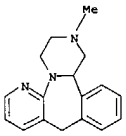
AB Mirtazapine, useful in treating depression (no data), was prepared by reacting pyridine I [R1 = CH2OH, CH2Cl, CH2Br, CH2I; R2 = NH2] with

L5 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)
II [R3 = Cl, F, Br, I] followed by treating the resulting piperazine III with H2SO4. The mirtazapine intermediate 1-(3-carboxypyridly-2)-4-methyl-2-phenylpiperazine may be made by hydrolyzing 1-(3-cyanopyridyl-2)-4-methyl-2-phenylpiperazine with KOH at a temp. of at least about 130°C. The present invention also relates to new processes for recrystn. of mirtazapine form crude mirtazapine.

IT **85650-52-8P**, Mirtazapine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(novel synthesis and **crystallization** of piperazine ring-containing compds. such as mirtazapine)

RN 85650-52-8 CAPLUS

CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT